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## Comparison of vomiting and diarrhoea frequency among dengue-infected patients

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### ABSTRACT

**Objective:** To compare the differences of vomiting and diarrhoea frequency between dengue with warning signs and severe dengue, and to describe the sites of mucosal bleeding among dengue-infected patients.

**Methods:** This was a retrospective cohort study which included patients with laboratory-confirmed dengue infection along with clinical diagnosis of dengue. Exclusion criteria were patients with haematological disorders or any other malignancy. The vomiting and diarrhoea frequency on each day (Day 1 to Day 5) between dengue with warning signs and severe dengue were compared by using Mann-Whitney *U* test. The different sites of mucosal bleeding were stratified according to the diagnoses and displayed by bar charts.

**Results:** Out of 1700 patients, 1003 (59.0%) had vomiting and 587 (34.5%) had diarrhoea. Both vomiting and diarrhoea frequency were not statistically different between dengue with warning signs and severe dengue from Day 1 to Day 5. Gum bleeding, hematemesis and menorrhagia were the only sites of mucosal bleeding seen in severe dengue for the first three days of illness. Hematemesis was seen only in severe dengue during the first day of illness but not in dengue with warning signs.

**Conclusions:** The frequency of vomiting and diarrhoea could not differentiate severe dengue from dengue with warning signs. Nevertheless, it is important to have high index of suspicion for dengue when patients are presented with diarrhoea. The different sites of mucosal bleeding could possibly predict severe dengue, especially hematemesis on the first three days of illness.

## 1. Introduction

More than 2.5 billion people, who constitute 40% of the world population, are at risk to the exposure of dengue infection. World Health Organization estimates 50 to 100 million dengue infections occur annually. Thus, an estimated 500000 people with severe dengue require hospitalization each year and about 2.5% of those affected die[1].

Dengue clinical manifestation is divided into three phases: febrile, critical and recovery phase. Critical phase which lasts up to 48 h, is the most important phase where the patient can either recover or die from the disease[2-4]. Therefore, it is important to identify the warning signs during the febrile phase which ranges from 2-7 days in order to

institute early treatment before complication develops[5]. "Persistent vomiting" was a non-specific warning sign and diarrhoea was a manifestation but not listed as warning sign in the guideline. This may be due to population variation whereby signs can be manifested differently[6,7]. Hence, the decision to admit patient into the hospital is at the clinician's discretion. This will lead to misdiagnosis and could lead to dengue mortality. Dengue prevalence is equivalently high in both urban and rural areas[8]. This emphasizes the need of accurate warning signs to predict the outcome of dengue infection whereby only minimal laboratory investigation is available in rural area.

Different clinical judgement will also lead to misclassification and this will in turn increase the burden of the disease by admitting too many patients into the ward for close monitoring. Hence, this study sought to compare the differences of vomiting and diarrhoea frequency between dengue with warning signs and severe dengue, and meanwhile to describe the sites of mucosal bleeding among dengue-infected patients.

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## 2. Materials and methods

### 2.1. Inclusion criteria

A retrospective cohort study was conducted from January to September 2014. All eligible patients' medical records who were admitted to Ampang Hospital were included in this study to obtain the frequency of vomiting and diarrhoea, and the sites of mucosal bleeding of each day. The clinical classification of dengue infection was based on the dengue guidelines published by World Health Organization[5]. All the medical records obtained from the census book in the Emergency Department of Ampang Hospital were dengue cases requiring admission.

The patients included in the study were either dengue immunoglobulin M (IgM) positive or nonstructural protein 1 (NS1) antigen positive, dengue IgM and NS1 antigen positive, with clinical diagnosis of dengue with warning signs or severe dengue (or its complication entity: severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding as evaluated by clinician and severe organ involvement). Dengue IgM results were obtained from the laboratory results of the hospital by tracing the medical records. NS1 antigen test results were obtained from the doctor's clerking of the patients' medical records as this test was performed at the Emergency Department by using rapid test kit. NS1 antigen positive results were included even though the dengue IgM test was negative because dengue IgM test can be negative if it was tested too early in the course of the disease. The clinical diagnoses were verified by using the classification guidelines[5].

The patients excluded from the study were patients with haematological disorders or any other malignancy. The developed warning signs such as vomiting and diarrhoea may be due to the disease or chemotherapy treatment.

### 2.2. Statistical analysis

The demography and proportion of clinical diagnoses were described accordingly. Patients who had vomiting and diarrhoea were described with count and percentage. The different sites of mucosal bleeding were stratified according to the diagnosis and displayed with bar charts. The median [interquartile range (IQR)] of vomiting and diarrhoea frequency on each day of illness (Day 1 to Day 5 of illness) and the respective count and percentage of missing data were described in Table 1.

**Table 1**

Vomiting and diarrhoea frequency from Day 1 to Day 5 of illness and the respective missing data. *n* (%).

Day	Vomiting, median (IQR)	Diarrhoea, median (IQR)	Vomiting*	Diarrhoea*
1	3 (3)	2 (1)	29 (1.7)	19 (1.1)
2	3 (3)	2 (1)	41 (2.4)	30 (1.8)
3	3 (3)	2 (1)	51 (3.0)	51 (3.0)
4	3 (3)	2 (1)	55 (3.2)	49 (2.9)
5	3 (3)	2 (1)	41 (2.4)	34 (2.0)

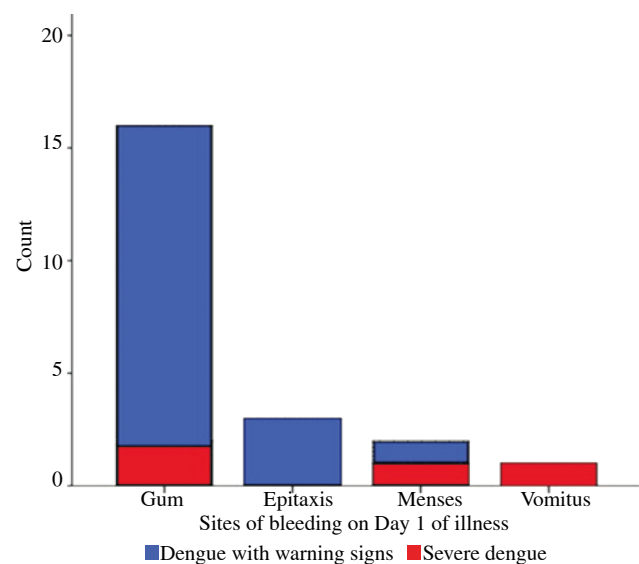
\*: Missing data.

The vomiting and diarrhoea frequency on each day of illness (Day 1 to Day 5 of illness) between dengue with warning signs and severe dengue was compared by using Mann-Whitney *U* test. The analysis was performed according to each day of illness when warning signs developed before the diagnosis of severe dengue being made. This was to ensure the prediction was fulfilled according to the days of illness prior to the development of severe dengue. The analysis was performed from Day 1 to Day 5 of illness. A two-tailed *P*-value of less than 0.05 was considered as statistically significant. SPSS version 20 was used in the analysis.

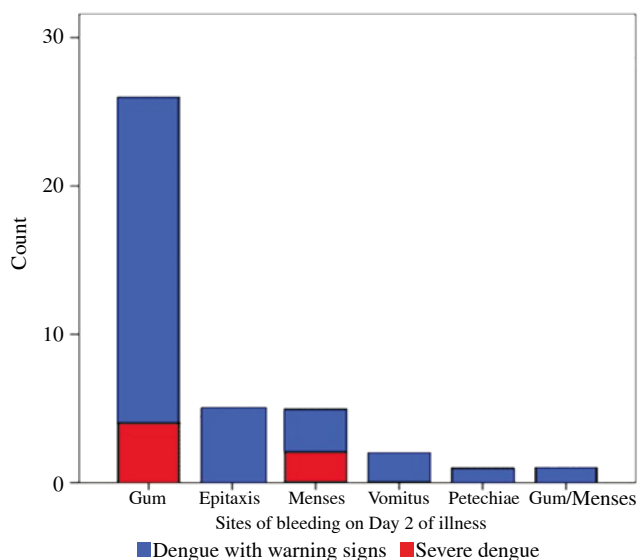
## 3. Results

The median age of the patients was 26 years old with IQR of 15 years old. Male patients were more than female ones with number of 1110 (65.3%) and 590 (34.7%), respectively. The number of patients who were diagnosed with severe dengue was 171 (10.1%) and out of which 24 (14.0%) did not develop any warning signs. Out of 1700 patients, 1003 (59.0%) had vomiting and 587 (34.5%) had diarrhoea. Table 1 shows the vomiting and diarrhoea frequency from Day 1 to Day 5 of illness and the respective missing data. The median and IQR of vomiting and diarrhoea were the same for all five days of illness as indicated in Table 1. The frequency of missing data was 3.2% or less.

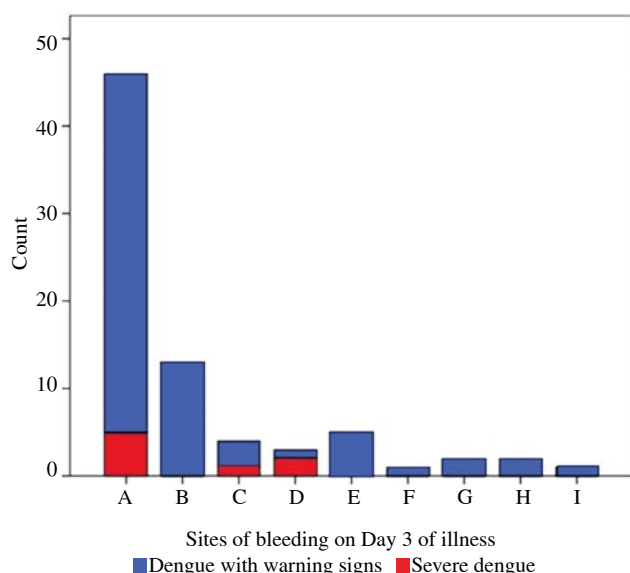
The mucosal bleeding occurred from Day 1 to Day eleven. Most of the mucosal bleeding occurred during Day four to Day six with a range of 91 to 116 cases. Gum bleeding alone was the most common mucosal bleeding with 280 out of 519 cases (54%). All the sites of the mucosal bleeding were stratified according to the final diagnosis as shown in Figures 1–5 from Day 1 to Day 5 of illness. The difference in frequency of vomiting and diarrhoea of all days were not statistically significant between dengue with warning signs and severe dengue as shown in Table 2.



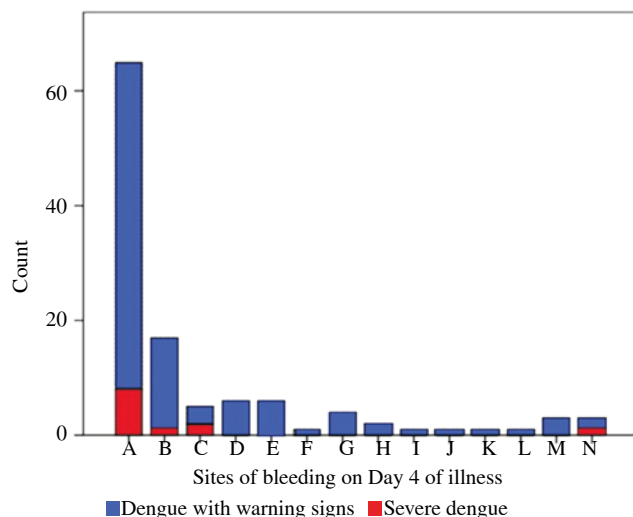
**Figure 1.** The different sites of mucosal bleeding on Day 1 of illness.



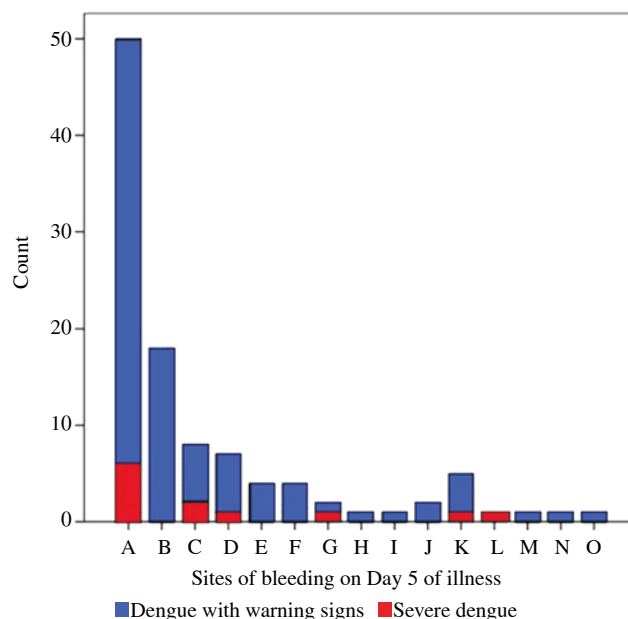
**Figure 2.** The different sites of mucosal bleeding on Day 2 of illness.



**Figure 3.** The different sites of mucosal bleeding on Day 3 of illness. A: Gum; B: Epitaxis; C: Menses; D: Vomitus; E: Petechiae; F: Hemoptysis; G: Hematuria; H: Gum/menses; I: Epitaxis/saliva.



**Figure 4.** The different sites of mucosal bleeding on Day four of illness. A: Gum; B: Epitaxis; C: Menses; D: Vomitus; E: Petechiae; F: Hemoptysis; G: Hematuria; H: Gum/menses; I: Gum/epitaxis; J: Epitaxis/menses; K: Epitaxis/sputum; L: Gum/vomitus; M: Sputum; N: Per vagina.



**Figure 5.** The different sites of mucosal bleeding on Day 5 of illness.

A: Gum; B: Epitaxis; C: Menses; D: Vomitus; E: Petechiae; F: Hematuria; G: Gum/menses; H: Gum/epitaxis; I: Gum/vomitus; J: Sputum; K: Per vagina; L: Saliva; M: Epitaxis/melena; N: Stool; O: Gum/petechiae.

**Table 2**

Comparison of vomiting and diarrhoea frequency from Day 1 to Day 5 of illness between dengue with warning signs and severe dengue.

Day	Vomiting, n (mean rank)				Diarrhoea, n (mean rank)			
	DWS	SD	U	P-value	DWS	SD	U	P-value
1	157 (94.58)	33 (97.06)	2446.0	0.81	62 (35.06)	10 (45.40)	221.0	0.13
2	303 (173.83)	40 (158.15)	5506.0	0.34	128 (71.15)	14 (74.68)	851.5	0.75
3	431 (244.49)	57 (244.61)	12277.5	1.00	213 (119.32)	26 (125.56)	2624.5	0.66
4	471 (263.84)	59 (278.73)	13114.0	0.47	269 (150.12)	31 (152.77)	4068.0	0.82
5	367 (202.56)	42 (226.30)	6812.5	0.21	218 (118.15)	18 (122.78)	1885.0	0.78

DWS: Dengue with warning signs; SD: Severe dengue; U: Mann-Whitney U test.

## 4. Discussion

The frequency of both vomiting and diarrhoea was the same from Day 1 to Day 5. There was no difference in vomiting and diarrhoea frequency between dengue with warning signs and severe dengue for the first five days of illness. Most of the mucosal bleeding occurred during Day 4 to Day 6 coinciding with the critical phase of the dengue progression. As the disease progressed to later days of illness, various sites of mucosal bleeding increased. Blood in the vomitus (hematemesis) on Day 1 was seen only in severe dengue cases. Only bleeding from gum, abnormal increasing amount of menses (menorrhagia) and hematemesis were seen on the first three days of severe dengue patients.

“Persistent vomiting” is a symptom among the warning signs that was loosely defined[6,9,10]. It is left to the clinicians to judge the number of vomiting frequency as “persistent” or not. Hence, clinicians tend to be more cautious in treating the patients by admitting them into the hospital for close monitoring rather than discharging them as outpatient care. This has explained why the warning signs have high sensitivity and low specificity and our study agreed that “vomiting” could not differentiate severe dengue from dengue with warning signs[11-14]. Unfortunately, this will

increase the health care burden since majority of the patients with warning signs would not develop complication and only 5% of all dengue-infected cases would progress to severe dengue[13]. A meta-analysis indicated that vomiting was able to predict the progression towards severe dengue[15]. However, the study did not take the day of illness into account when the symptom occurred in their meta-analysis[15]. Ideally, the meta-analysis should be stratified according to the day of illness so that it could allow appropriate prediction of the disease outcome.

Vomiting is the commonest among other warning signs of dengue infection[16]. However, many previous studies indicated that abdominal tenderness or pain was the commonest. This could be explained by the different underlying population which manifests symptoms differently or by clinical practice variation with different emphasis on the warning signs in their studies[7,11,17]. In fact, meta-analysis indicated that abdominal pain was a better predictor than vomiting with odds ratio of 2.278 (95% CI: 1.631, 3.182) compared to vomiting with odds ratio of 1.692 (95% CI: 1.256, 2.280)[15].

Diarrhoea is unlikely to be able to predict severe dengue[15]. Furthermore, not many studies described diarrhoea as a common symptom[18-27]. Diarrhoea was analysed in our study because it was noted to be a consistent symptom complained by the dengue-infected patients at our local setting. A similar proportion of diarrhoea symptom was found in a study conducted in Singapore[28]. Seet *et al.* explained that diarrhoea could increase vascular leakage and lead to osmotic diarrhoea. However, there is no evidence as yet to explain the symptom[28].

Interestingly, diarrhoea was one of the predominating symptoms in Malaysia and Singapore but not seen elsewhere such as Bangladesh, France, India, Thailand, Taiwan, Sri Lanka and Pakistan[19-27]. The different predominant circulating serotype of dengue virus in different location could possibly explain the differences in the frequency of diarrhoea. Endy *et al.* and Malavige *et al.* found that DEN-3 was the predominant circulating serotype in Thailand and Sri Lanka, respectively[23,27].

However, study by Seet *et al.* has shown to have serotype DEN-2 predominantly in Singapore which was the same finding as Thomas *et al.* in France[21,28]. Furthermore, large-scale study by Sirivichayakul *et al.* reported around 35% of diarrhoea seen in DEN-3 and DEN-4 infected patients as oppose to about 20%-23% of diarrhoea reported in DEN-1 and DEN-2 infected patients[24]. These conflicting results could not explain the diarrhoea frequency in different serotypes of dengue virus. Perhaps, a more complex virus and host interaction could be the underlying pathogenesis for the occurrence of diarrhoea as predominating symptom in different locations.

The frequency of each site of mucosal bleeding generally agreed to previous study[29]. Hematemesis on Day 1 and Day 3 of illness might be a predictor of severe dengue. This is evident in previous study where hematemesis has an odds ratio of 6.174 (95% CI: 2.660, 14.334) for predicting severe dengue[15]. Other common sites of mucosal bleeding were the gum and menorrhagia but it is unlikely to

be predictable since much of the dengue with warning signs did not progress to severe dengue.

Limitation of this study is inconsistent diarrhoea symptom as it is currently not a warning sign and clinician might disregard it as acute gastroenteritis. Since there is a limitation in the warning signs whereby clinical judgement is necessary, it is subjected to bias. The diagnostic test for dengue infection might produce false positive or false negative. This is seen in the NS1 antigen rapid test kit where false negative can occur. Hence, a repeat of the test by using dengue IgM is necessary to confirm the case if dengue infection is clinically suspected. In some of the suspected cases, tests were not repeated even the final diagnosis was still dengue infection. This could be explained by the massive outbreak of dengue infection whereby the test for dengue might be insufficient. Some of the dengue IgM serology was tested negative but no repeat of the test was done while the final diagnosis remained as dengue. Hence, underestimate of the disease was unavoidable and it was possible to bias the result of this study.

Further study may overcome some issues encountered in our study. Future studies shall have prospectively collected data whereby the diarrhoea and its frequency can be obtained accurately. The diagnostic test for dengue (case definition) must also be precise as our study was depended on the clinicians' decision for testing the disease and this has led to variation in the laboratory diagnosis. Once the issues have been addressed in the study design, other consideration for future studies is to analyse warning signs or the sites of mucosal bleeding by multivariate analysis to account for possible confounding factors or effect modifiers. In our data acquired, no details on secondary dengue were documented clearly. This is one of the most important factors to be considered in the analysis because secondary dengue can have more severe manifestation[30]. Other factors such as the serotype of the dengue should also be tested and included into the multivariate analysis[30].

In conclusion, the frequency of vomiting and diarrhoea could not differentiate severe dengue from dengue with warning signs. Nevertheless, it is important to have high index of suspicion for dengue when patient is presented with diarrhoea, which though is not a warning sign, especially in an endemic country. The different sites of mucosal bleeding could possibly predict severe dengue especially hematemesis in the first three days of illness.

### Conflict of interest statement

We declare that we have no conflict of interest.

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